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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/588,186	08/02/2006	Laurence Hermitte	0528-1187	6791

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EXAMINER	
BROWE, DAVID	
ART UNIT	PAPER NUMBER
1616	

NOTIFICATION DATE	DELIVERY MODE
06/03/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DocketingDept@young-thompson.com

Office Action Summary	Application No.	Applicant(s)	
	10/588,186	HERMITTE ET AL.	
	Examiner	Art Unit	
	DAVID M. BROWE	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 April 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-20 are pending.

Applicants timely submission of amendments and arguments on April 20, 1010 in response to the Non-Final Office Action of January 20, 2010 is acknowledged.

Withdrawal of Prior Claim Rejections - 35 USC § 112 2nd Paragraph

Claim 12 has been satisfactorily amended to remove the indefinite recitation of the "use of a gel". Therefore, the 35 USC § 112 2nd Paragraph rejection presented in the Office Action of January 20, 2010 is hereby withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ågerup (U.S. Patent No. 5,827,937), in view of Miller *et al.* (U.S. Patent No. 6,174,999).

Applicant Claims

Applicants claim a process for the production of a biocompatible crosslinked gel comprising: *a)* starting a crosslinking reaction of a predetermined quantity of at least one biocompatible polymer in solution by the addition of a quantity of crosslinking agent in a reaction mixture; *b)* crosslinking said quantity of polymer; *c)* diluting the reaction mixture to decrease the concentration of polymer in solution, and adding a supplemental quantity of polymer of a molecular weight higher than 500,000 Da in solution, and continuing crosslinking; and *d)* stopping the crosslinking reaction by eliminating the crosslinking agent. The crosslinking reaction can be initiated in a basic or acidic medium; a supplemental quantity of crosslinking agent is added during the step of adding a supplemental quantity of polymer; and the step of stopping the

crosslinking reaction is carried out by dialysis. The polymers are of natural origin and selected from the group consisting of hyaluronic acid, chondroitin sulfate, keratin, keratin sulfate, heparin, heparin sulfate, cellulose and its derivatives, alginates, xanthane, carrageenan, proteins, and nucleic acids, wherein at least one polymer not naturally present in the human body is crosslinked with at least one polymer naturally present in the human body. The crosslinking agent is a bifunctional or polyfunctional molecule comprising components selected from the group consisting of epoxys, epihalohydrins, and divinylsulfone.

Applicants also claim a gel prepared by the process that comprises at least one dispersed active agent.

Applicants further claim a method to separate, replace, or fill a biological tissue or increase the volume of said tissue or to supplement or replace a biological fluid, comprising injecting the gel into said tissue.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Ågerup discloses a process for the production of a biocompatible crosslinked gel comprising: *a)* starting a crosslinking reaction of a predetermined quantity of at least one biocompatible polymer in solution by the addition of a quantity of crosslinking agent; *b)* crosslinking said quantity of polymer; and *c)* diluting the reaction mixture to decrease the concentration of polymer in solution, supplementing the polymer concentration in solution and accelerating the rate of the crosslinking reaction (which would encompass adding supplemental quantities of polymer and crosslinking agent to the diluted reaction medium); and *d)* crosslinking to a viscoelastic gel (Col. 1, lns. 4-12; Col. 2, lns. 11-15,

48-67; Col. 3, lns. 1-2, 25-60; Col. 4, lns. 1-3, 6-30). The crosslinking reaction can be initiated in a basic or acidic medium, and the step of increasing the polymer concentration and crosslinking reaction rate need not necessarily proceed under the exact same conditions as when initiating the crosslinking (Col. 3, lns. 32-40; Col. 4, lns. 22-30). The polymers can be of natural origin and selected from the group consisting of hyaluronic acid, chondroitin sulfate, keratin, keratin sulfate, heparin, heparin sulfate, cellulose and its derivatives, alginates, xanthane, carrageenan, proteins, and nucleic acids, wherein at least one polymer not naturally present in the human body is crosslinked with at least one polymer naturally present in the human body (Col. 4, lns. 1-3, 6-9; Col. 7, lns. 21, 35, 48-49, 58-59). The crosslinking agent is a bifunctional or polyfunctional molecule comprising components selected from the group consisting of epoxides, such as epihalohydrins; and divinylsulfone (Col. 4, lns. 10-21).

Ågerup also discloses a gel prepared by the process that comprises at least one dispersed active agent; and is used to separate, replace, or fill a biological tissue or increase the volume of said tissue or else to supplement or replace a biological fluid (Col. 2, lns. 17-19, 24-38; Col. 4, lns. 49-55; Col. 5, lns. 49-60; Col. 6, lns. 12-24).

Ågerup further discloses a method to separate, replace, or fill a biological tissue or increase the volume of said tissue or to supplement or replace a biological fluid, comprising administering the gel into said tissue (Col. 4, lns. 34-36; Col. 6, lns. 12-24).

Miller *et al.* disclose a process of preparing a biocompatible crosslinked polysaccharide gel that includes stopping a reaction by eliminating a non-polymeric

reactant from the reaction medium by dialysis, according to standard practice, prior to use (Col. 1, lns. 13-15; Col. 2, lns. 32-36; Col. 6, lns. 39-42).

Ascertainment of the Difference Between the Scope of the Prior Art and the Claims (MPEP §2141.012)

Ågerup does not explicitly disclose a crosslinking process that specifically includes *i)* adding supplemental quantities of polymer and crosslinking agent to the diluted reaction medium and *ii)* stopping the reaction specifically by dialysis. These deficiencies is cured by the teaching of Ågerup and Miller *et al.*

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of the present invention to combine the respective teachings of Ågerup and Miller *et al.* outlined *supra* to devise applicants claimed invention. Ågerup discloses a process for preparing a biocompatible cross-linked gel utilizing a dilution-concentration cross-linking technique that enables more optimal control of cross-link coupling site architecture; the gel products thus produced do not cause interfering or negative volume effects when administered in vivo, and better retain and provide sustained-release delivery of active substances. Since Ågerup specifies that diluting the reaction mixture to decrease the concentration of polymer in solution is accompanied by supplementing the polymer concentration in solution and accelerating the rate of the cross-linking reaction; and since Miller *et al.* disclose the step of preparing purified polymer mixtures, for direct use in drug delivery, by eliminating unreacted "activating agent" by dialysis,

one of ordinary skill in the art would be motivated to devise a cross-linking reaction that specifically included *i)* adding supplemental quantities of polymer and cross-linking agent to the diluted reaction medium (thus, achieving increased polymer concentration and accelerated rate of cross-linking) and *ii)* stopping the reaction specifically by dialysis, with the reasonable expectation that such a technique would successfully produce a cross-linked biocompatible gel in optimal purified condition for direct *in vivo* use in providing a better sustained-release drug delivery profile without causing any interfering or negative volume effects.

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

Applicant's arguments filed April 20, 2010 have been fully considered but they are not persuasive.

Applicants assert that "*In particular, Ågerup fails to teach or suggest a process that includes cross-linking the polymer, and adding supplemental polymer while diluting the reaction mixture and continuing the cross-linking reaction. In contrast to Ågerup, the*

presently claimed process does not stop the cross-linking reaction when the supplemental amount of polymer having a specific molecular weight is added. The supplemental addition results in a dilution of the reaction mixture such that the overall concentration of polymer in the mixture decreases." Respectfully, though, the Examiner, from the disclosure of Ågerup alone, cannot agree with the assertion that Ågerup fails to teach or suggest applicants claimed process. Ågerup teaches a process that includes cross-linking the polymer, "stearically hindering" the cross-linking reaction, re-introducing "stearically unhindered" conditions, and continuing the cross-linking reaction. Ågerup explains that "stearically hindering" means diluting the reaction mixture; this need not stop the reaction, only lower the concentration of polymer (Col. 3, lns. 25-30, 43-47). Re-introducing "stearically unhindered" conditions, according to Ågerup, should be "interpreted broadly" to mean anything that accomplishes a higher concentration of the polymer in said medium and enables a more rapid reaction to take place relative to the stearically hindered condition (Col. 3, lns. 32-33, 37-39, 52-53). Although Ågerup suggests, as particular examples, increasing polymer concentration by evaporating or dialyzing the aqueous medium, one of ordinary skill in the art would recognize that accomplishing a higher concentration of the polymer can also be done simply by adding more polymer, and that enabling a more rapid reaction can be done by adding more polymer and more cross-linking agent. Thus, respectfully, applicants arguments are not found persuasive and the rejection is maintained.

Applicants further state that "*The degree of cross-linking thus varies in the final gel which is constituted by strongly cross-linked hubs interconnected by a gel which is*

less cross-linked." Respectfully, though, the Examiner, from the disclosure of Ågerup alone, cannot agree with the assertion that Ågerup fails to teach or suggest applicants claimed gel. Ågerup further explains that the re-introduced sterically unhindered condition need not be exactly the same conditions as were used when initiating the cross-linking reaction (Col. 3, lns. 35-36); thus, the overall polymer concentration can be decreased. A partially cross-linked gel is obtained before the dilution step (Col. 2, lns. 37-38), and one of ordinary skill in the art would expect that if the re-introduced sterically unhindered condition involves an overall lower polymer concentration compared to that used when initiating the cross-linking reaction, the final gel would be characterized by a varied degree of cross-linking with strongly cross-linked hubs interconnected by a gel which is less cross-linked. Thus, respectfully, applicants arguments are not found persuasive and the rejection is maintained.

Applicants assert that "*As detailed in the specification, under these conditions, the polymer chains have new cross-linking sites which will react with the residual cross-linkage agent*". Respectfully, though, the Examiner, from the disclosure of Ågerup alone, cannot agree that this property is sufficient grounds to withdrawal the rejection. Ågerup also states that their process enables the final cross-linking reaction to take place with new reaction sites involved (Col. 3, lns. 29-31), which will react with the residual cross-linkage agent (Col. 3, lns. 57-60). Thus, respectfully, applicants arguments are not found persuasive and the rejection is maintained. However, the Examiner allows that the rejection can be overcome if applicants can provide support in the form of comparative data that establishes factual evidence that the respective polymer gels

produced by their claimed method and the Ågerup method, as outlined herein, are indeed patentably distinct products.

Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Inquiries

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DAVID M. BROWE whose telephone number is 571-270-1320. The examiner can normally be reached on Monday-Friday 7:30AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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